Drug Class Review
on
ACE Inhibitors

Update #3: Preliminary Scan Report 2

February 2008

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Oregon Evidence-based Practice Center
Oregon Health & Science University
Mark Helfand, MD, MPH, Director
Marian S McDonagh, Principal Investigator,
Drug Effectiveness Review Project

Update scan prepared by Susan Severance, MPH

OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations' consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the FDA or Health Canada since the last report. Other important studies could exist.

Date of Last Update

June 2005 (searches through February 2005)

Date of Last Update Scan

February 2007

Scope and Key Questions

The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

Key Questions

1. For adult patients with essential hypertension, heart failure, high cardiovascular risk factors, diabetic nephropathy, nondiabetic nephropathy, or recent myocardial infarction, do angiotensin converting enzyme (ACE) inhibitors differ in effectiveness?

2. For adult patients with essential hypertension, heart failure, high cardiovascular risk factors, diabetic nephropathy, nondiabetic nephropathy, or recent myocardial infarction, do ACE inhibitors differ in safety or adverse events?

3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or co-morbidities for which one ACE inhibitor is more effective or associated with fewer adverse events?

Inclusion Criteria

<u>Populations</u>

Adult patients with any of the following indications:

- Hypertension without compelling indications. This refers to patients with hypertension who do not have any of the following indications:
    a. a history of coronary heart disease (CHD)
    b. other cardiovascular diseases (CVD), such as cerebrovascular (carotid) disease, peripheral vascular disease, or a history of stroke
    c. other risk factors for CAD/CVD, such as diabetes, smoking or hyperlipidemia
    d. renal insufficiency
- Hypertension with compelling indications. This refers to patients with hypertension who also have one of the conditions listed above.
- High cardiovascular risk. This group includes patients who have a history of CHD/CVD, or a combination of other risk factors for CHD/CVD, such as diabetes, smoking, and hyperlipidemia. These patients may or may not have hypertension as well.
- Recent myocardial infarction. This group includes patients who have had a recent myocardial infarction and who have normal left ventricular function or asymptomatic left ventricular dysfunction.
- Heart failure. This group includes patients who have symptomatic heart failure due to left ventricular systolic dysfunction, with or without hypertension.
- Diabetic nephropathy. This group includes patients with Type 1 or Type 2 diabetes who have laboratory evidence of nephropathy, such as albuminuria or decreased creatinine clearance.

Interventions

- benazepril
- captopril
- cilazapril
- enalapril
- fosinopril
- lisinopril
- moexipril
- quinapril
- ramipril
- perindopril
- trandolapril

Effectiveness outcomes

Effectiveness measures varied according to the clinical condition:

Hypertension

- All-cause and cardiovascular mortality
- Cardiovascular events (stroke, myocardial infarction, or development of heart failure)
- End-stage renal disease (including dialysis or need for transplantation) or clinically significant and permanent deterioration of renal function (increase in serum creatinine or decrease in creatinine clearance)
- Quality-of-life

(Trials that focused on blood pressure reduction but not on any health outcomes were excluded from the effectiveness review)

High cardiovascular risk

- All-cause and cardiovascular mortality
- Cardiovascular events (stroke, myocardial infarction, or development of heart failure)

Recent myocardial infarction

- All-cause and cardiovascular mortality
- Cardiovascular events (usually, development of heart failure)

Heart failure

- All-cause or cardiovascular mortality
- Symptomatic improvement (heart failure class, functional status, visual analogue scores)
- Hospitalizations for heart failure

Diabetic nephropathy/non-diabetic nephropathy

- End-stage renal disease (including dialysis or need for transplantation)
- Clinically significant and permanent deterioration of renal function (increase in serum creatinine or decrease in creatinine clearance)

Safety outcomes

- Withdrawals
- Withdrawals due to adverse effects
- Specific adverse effects or withdrawals due to specific adverse events, for example, symptomatic hypotension

Study designs

1. Randomized controlled trials that compared one of the included ACE inhibitors to another.
2. Systematic reviews of the clinical effectiveness or adverse event rates of ACE inhibitors for included clinical conditions that reported an included outcome.
3. Large (> 100 patients) placebo-controlled trials for included clinical conditions that reported an included outcome.
4. Randomized controlled trials and large, good-quality observational studies that evaluated adverse event rates for one or more of the included ACE Inhibitors.

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations from January 2007 through February Week 2, 2008, using terms for included drugs and indications, and limits for humans, English language, and randomized controlled trials or controlled clinical trials. We also searched FDA (http://www.fda.gov/medwatch/safety.htm) and Health Canada (http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2008/index_e.html) websites for identification of new drugs,

indications, and safety alerts. All citations were imported into an electronic database (EndNote 9.0) and duplicate citations were removed.

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

Overview

Searches resulted in 149 citations. Of those, there are 13 new potentially relevant trials (see Appendix A, attached). Take together with the 23 trials identified in the first preliminary update scan, now there are a total of 36.

New Drugs

No new ACE Inhibitors were identified. Ramipril (Altace) is now available in tablet form.

New Indications

No new indications were identified.

New Safety Alerts

New information was added to the product safety labels for 3 ACE Inhibitors. Details of these changes are listed in the table below.

ACE Inhibitor	Date of change	Details of new safety information
lisinopril	2/07	Fetal/Neonatal Morbidity and Mortality Pregnancy: Female patients of childbearing age should be told about the consequences of exposure to ACE inhibitors during pregnancy. These patients should be asked to report pregnancies to their physicians as soon as possible. .....In a published retrospective epidemiological study, infants whose mothers had taken an ACE inhibitor during their first trimester of pregnancy appeared to have an increased risk of major congenital malformations compared with infants whose mothers had not undergone first trimester exposure to ACE inhibitor drugs. The number of cases of birth defects is small and the findings of this study have not yet been repeated.

ACE Inhibitor	Date of change	Details of new safety information
benazepril	2/07	BOXED WARNING: Use in Pregnancy: When used in pregnancy, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, Lotensin should be discontinued as soon as possible. Warning: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, Lotensin should be discontinued as soon as possible and monitoring of the fetal development should be performed on a regular basis. In addition, use of ACE inhibitors during the first trimester of pregnancy has been associated with a potentially increased risk of birth defects. In women planning to become pregnant, ACE inhibitors (including Lotensin) should not be used. Women of child-bearing age should be made aware of the potential risk and ACE inhibitors (including Lotensin)..... Precautions: Information for Patients, Pregnancy: Pregnancy Category D
enalapril	10/07	WARNINGS: Intestinal Angioedema Intestinal angioedema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior history of facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan or ultrasound, or at surgery, and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain... WARNINGS: Fetal/Neonatal Morbidity and Mortality ...In a published restrospective epidemiological study, infants whose mothers had taken an ACE inhibitor drug during the first trimestrer of pregnancy appeared to have an increased risk of major congenital malformations compared with infants whose mothers had not undergone first trimester exposure to ACE inhibitor drugs. The number of cases of birth defects is small and the findings of this study have not yet been repeated...

ACE Inhibitor	Date of change	Details of new safety information
lisinopril	10/07	WARNINGS: Anaphylactoid Reactions During Membrane Exposure Sudden and potentially life threatening anaphylactoid reactions have been reported in some patients dialyzed with high-flux membranes (e.g., AN69®*) and treated concomitantly with an ACE inhibitor. In such patients, dialysis must be stopped immediately, and aggressive therapy for anaphylactoid reactions must be initiated. Symptoms have not been relieved by antihistamines in these situations. In these patients, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

Appendix A. Abstracts of potentially relevant new trials of ACE Inhibitors

Brugts, J. J., E. Boersma, et al. (2007). "The cardioprotective effects of the angiotensin-converting enzyme inhibitor perindopril in patients with stable coronary artery disease are not modified by mild to moderate renal insufficiency: insights from the EUROPA trial." Journal of the American College of Cardiology 50(22): 2148-55.

OBJECTIVES: This study sought to examine whether the cardioprotective effects of angiotensin-converting enzyme (ACE) inhibitor therapy by perindopril are modified by renal function in patients with stable coronary artery disease. BACKGROUND: A recent study reported that an impaired renal function identified a subgroup of patients with stable coronary artery disease more likely to benefit from ACE inhibition therapy. In light of the growing interest in tailored therapy for targeting medications to specific subgroups, remarks on the consistency of the treatment effect by ACE inhibitors are highly important. METHODS: The present study involved 12,056 patients with stable coronary artery disease without heart failure randomized to perindopril or placebo. Estimated glomerular filtration rate (eGFR) was calculated using the abbreviated Modification of Diet in Renal Disease equation. Cox regression analysis was used to estimate multivariable-adjusted hazard ratios. RESULTS: The mean eGFR was 76.2 (+/-18.1) ml/min/1.73 m2. During follow-up, the primary end point (cardiovascular death, nonfatal myocardial infarction, or resuscitated cardiac arrest) occurred in 454 of 5,761 patients (7.9%) with eGFR > or =75 and in 631 of 6,295 patients (10.0%) with eGFR <75. Treatment benefits of perindopril were apparent in both patient groups either with eGFR > or =75 (hazard ratio 0.77; 95% confidence interval 0.64 to 0.93) or eGFR <75 (hazard ratio 0.84; 95% confidence interval 0.72 to 0.98). We observed no significant interaction between renal function and treatment benefit (p = 0.47). Using different cutoff points of eGFR at the level of 60 or 90 resulted in similar trends. CONCLUSIONS: The treatment benefit of perindopril is consistent and not modified by mild to moderate renal insufficiency.

Cooper-DeHoff, R. M., Q. Zhou, et al. (2007). "Influence of Hispanic ethnicity on blood pressure control and cardiovascular outcomes in women with CAD and hypertension: findings from INVEST." Journal of Women's Health 16(5): 632-40.

BACKGROUND: Prospective data regarding blood pressure (BP) control and cardiovascular (CV) outcomes in Hispanic women are lacking. METHODS: We analyzed 5017 Hispanic and 4710 non-Hispanic white hypertensive women with coronary artery disease (CAD) in the INternational VErapamil SR/Trandolapril STudy (INVEST) to determine the impact of baseline characteristics and BP control on CV outcomes. RESULTS: At baseline, Hispanic women were younger and a had lower prevalence of most established CV risk factors than non-Hispanic white women. At 24 months, BP control (< 140/90 mm Hg) was achieved in 75% of Hispanic and 68% of non-Hispanic white women, (p < 0.001), with most women, regardless of ethnicity, requiring > or =2 antihypertensive agents. Following 26,113 patient-years of follow-up, the primary outcome (first occurrence of nonfatal myocardial infarction [MI], nonfatal stroke, or all cause death) occurred in 5.7% of Hispanic and 12.3% of non-Hispanic white women (adjusted HR = 0.84, 95% CI = 0.71-0.98, p = 0.03). There was no difference in outcome in either group of women comparing the randomized antihypertensive treatment

strategies. CONCLUSIONS: Despite accounting for a lower risk profile, deployment of protocol-based antihypertensive treatment regimens resulted in superior BP control and fewer CV events in Hispanic women compared with non-Hispanic white women.

Coppo, R., L. Peruzzi, et al. (2007). "IgACE: a placebo-controlled, randomized trial of angiotensin-converting enzyme inhibitors in children and young people with IgA nephropathy and moderate proteinuria.[see comment]." Journal of the American Society of Nephrology 18(6): 1880-8.

This European Community Biomedicine and Health Research-supported, multicenter, randomized, placebo-controlled, double-blind trial investigated the effect of an angiotensin-converting enzyme inhibitor (ACE-I) in children and young people with IgA nephropathy (IgAN), moderate proteinuria (>1 and <3.5 g/d per 1.73 m(2)) and creatinine clearance (CrCl) >50 ml/min per 1.73 m(2). Sixty-six patients who were 20.5 yr of age (range 9 to 35 yr), were randomly assigned to Benazepril 0.2 mg/kg per d (ACE-I) or placebo and were followed for a median of 38 mo. The primary outcome was the progression of kidney disease, defined as >30% decrease of CrCl; secondary outcomes were (1) a composite end point of >30% decrease of CrCl or worsening of proteinuria until > or =3.5 g/d per 1.73 m(2) and (2) proteinuria partial remission (<0.5 g/d per 1.73 m(2)) or total remission (<160 mg/d per 1.73 m(2)) for >6 mo. Analysis was by intention to treat. A single patient (3.1%) in the ACE-I group and five (14.7%) in the placebo group showed a worsening of CrCl >30%. The composite end point of >30% decrease of CrCl or worsening of proteinuria until nephrotic range was reached by one (3.1%) of 32 patients in the ACE-I group, and nine (26.5%) of 34 in the placebo group; the difference was significant (log-rank P = 0.035). A stable, partial remission of proteinuria was observed in 13 (40.6%) of 32 patients in the ACE-I group versus three (8.8%) of 34 in the placebo group (log-rank P = 0.033), with total remission in 12.5% of ACE-I-treated patients and in none in the placebo group (log-rank P = 0.029). The multivariate Cox analysis showed that treatment with ACE-I was the independent predictor of prognosis; no influence on the composite end point was found for gender, age, baseline CrCl, systolic or diastolic BP, mean arterial pressure, or proteinuria.

Daly, C. A., P. Hildebrandt, et al. (2007). "Adverse prognosis associated with the metabolic syndrome in established coronary artery disease: data from the EUROPA trial." Heart 93(11): 1406-11.

OBJECTIVE: To assess the prevalence of metabolic syndrome, and its effect on cardiovascular morbidity and mortality in patients with established coronary disease and to explore the inter-relationships between metabolic syndrome, diabetes, obesity and cardiovascular risk. METHODS: The presence of metabolic syndrome was determined in 8397 patients with stable coronary disease from the European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease, with mean follow-up of 4.2 years. Metabolic syndrome was defined using a modified version of the National Cholesterol Education Programme criteria. RESULTS: Metabolic syndrome was present in 1964/8397 (23.4%) of the population and significantly predicted outcome; relative risk (RR) of cardiovascular mortality = 1.82 (95% CI 1.40 to 2.39); and fatal and non-fatal myocardial infarction RR = 1.50 (95% CI 1.24 to 1.80). The association with adverse outcomes remained significant after adjustment, RR of cardiovascular mortality after adjustment for conventional risks and diabetes = 1.39 (95% CI 1.03 to 1.86). In

comparison with normal weight subjects without diabetes or metabolic syndrome, normal weight dysmetabolic subjects (with either diabetes or metabolic syndrome) were at substantially increased risk of cardiovascular death (RR = 4.05 (95% CI 2.38 to 6.89)). The relative risks of cardiovascular death for overweight and obese patients with dysmetabolic status were nominally lower (RR = 3.01 (95% CI 1.94 to 4.69) and RR = 2.35 (95% CI 1.50 to 3.68), respectively). CONCLUSIONS: Metabolic syndrome is associated with adverse cardiovascular outcome, independently of its associations with diabetes and obesity. A metabolic profile should form part of the risk assessment in all patients with coronary disease, not just those who are obese.

Eveson, D. J., T. G. Robinson, et al. (2007). "Lisinopril for the treatment of hypertension within the first 24 hours of acute ischemic stroke and follow-up.[see comment]." American Journal of Hypertension 20(3): 270-7.

BACKGROUND: Hypertension immediately after acute ischemic stroke is associated with impaired morbidity and mortality, although there are few data on antihypertensive use immediately after ictus. This randomized, double-blinded, placebo-controlled, parallel-group study explored the hemodynamic effect and safety of oral lisinopril initiated within 24 h after an ictus. METHODS: Forty hypertensive (systolic blood pressure [BP] >/=140 or diastolic BP >/=90 mm Hg) acute ischemic stroke patients (14 lacunar, 13 partial anterior, 7 total anterior, 6 posterior circulation infarct) were randomized to 5 mg of oral lisinopril (n = 18) or matching placebo (n = 22). Dose was increased to 10 mg (or 2 x placebo) on day 7 if casual systolic BP was >/=140 mm Hg and continued to day 14. After the initial dose, automated BP levels were monitored for 16 h. The BP levels and stroke outcome measures were assessed at day 14, and all patients were followed to day 90. RESULTS: At h 4 after the first dose, systolic/diastolic BP change was -20 +/- 21/-6 +/- 10 mm Hg (mean +/- SE) in the lisinopril group and 1 +/- 11/0 +/- 8 mmHg in the placebo group (group differences: systolic BP, $P < .05$; diastolic BP, $P = .07$). With a daily dosing regime, systolic BP, mean arterial pressure (MAP), diastolic BP, and pulse pressure (PP) were significantly lower in the lisinopril group compared to the placebo group at day 14 ($P < .01$). Neurologic and functional measures were similar between groups at follow-up. CONCLUSIONS: Lisinopril, even at small dosages, is well tolerated and an effective hypotensive agent after acute ischemic stroke, gradually reducing BP by 4 h after oral first-dose administration. Oral lisinopril is now being studied in a larger outcome-based trial in acute hypertensive stroke patients.

Gianni, M., J. Bosch, et al. (2007). "Effect of long-term ACE-inhibitor therapy in elderly vascular disease patients.[see comment]." European Heart Journal 28(11): 1382-8.

AIMS: Cardiovascular (CV) disease is the leading cause of death in the elderly. The use of ACE-inhibitors in elderly patients with chronic stable vascular disease has not been previously reported. METHODS AND RESULTS: The HOPE trial evaluated the effects of ramipril and vitamin E in high-risk vascular disease patients. We report the effects of ramipril in the elderly HOPE study patients, defined as those > or =70 years of age. A total of 2755 elderly patients with vascular disease or diabetes and at least one additional CV risk factor and without heart failure or low ejection fraction were randomized to ramipril 10 mg daily or placebo. Those assigned to ramipril had fewer major vascular events compared to those assigned to placebo [18.6 vs. 24.0%, hazard ratio (HR) = 0.75, $P = 0.0006$], CV deaths (9.3 vs. 13.0%, HR = 0.71, $P = 0.003$), myocardial infarctions

(12.0 vs. 15.6%, HR = 0.75, P = 0.006), and strokes (5.4 vs. 7.7%, HR = 0.69, P = 0.013). Treatment was safe and generally well tolerated. CONCLUSION: Ramipril reduces the risk of major vascular events in elderly patients with vascular disease and is safe and well tolerated by most.

Held, C., H. C. Gerstein, et al. (2007). "Glucose levels predict hospitalization for congestive heart failure in patients at high cardiovascular risk.[see comment]." Circulation 115(11): 1371-5.

BACKGROUND: Patients with diabetes mellitus (DM) are at high risk of developing congestive heart failure (CHF). However, the relationships between glucose levels and CHF in people with or without a history of DM have not been well characterized. METHODS AND RESULTS: We evaluated the associations between fasting plasma glucose and risk of hospitalization for CHF during follow-up in patients at high cardiovascular risk and without CHF enrolled in a large-scale clinical trials program. Baseline fasting plasma glucose levels were assessed in 31,546 high-risk subjects with > or = 1 coronary, peripheral, or cerebrovascular disease or DM with end-organ damage who are participating in 2 ongoing parallel trials evaluating the effects of telmisartan, ramipril, or their combination (Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial [ONTARGET]; n=25,620) and the effects of telmisartan against placebo in angiotensin-converting enzyme-intolerant patients (Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease [TRANSCEND]; n=5926). Interim analyses blinded for randomized treatment were performed to compare baseline fasting plasma glucose with the adjusted CHF event rate at a mean follow-up of 886 days. Multivariable Cox regression models were performed, and associations were reported as hazard ratios and 95% confidence intervals. Among all subjects (mean age, 67 years; 69% men), of whom 11,708 (37%) had known DM and 1006 (3.2%) had newly diagnosed DM at baseline, 668 patients were hospitalized for CHF during follow-up. After adjustment for age and sex, a 1-mmol/L-higher fasting plasma glucose was associated with a 1.10-fold-increased risk of CHF hospitalization (95% confidence interval, 1.08 to 1.12; P<0.0001). The association persisted after adjustment for age, sex, smoking, previous myocardial infarction, hypertension, waist-to-hip ratio, creatinine, DM, and use of aspirin, beta-blockers, or statins (hazard ratio, 1.05; 95% confidence interval, 1.02 to 1.08; P<0.001). CONCLUSIONS: Fasting plasma glucose is an independent predictor of hospitalization for CHF in high-risk subjects. These data provide theoretical support for potential direct beneficial effects of glucose lowering in reducing the risk of CHF and suggests the need for specific studies targeted at this issue.

Hou, F. F., D. Xie, et al. (2007). "Renoprotection of Optimal Antiproteinuric Doses (ROAD) Study: a randomized controlled study of benazepril and losartan in chronic renal insufficiency." Journal of the American Society of Nephrology 18(6): 1889-98.

The Renoprotection of Optimal Antiproteinuric Doses (ROAD) study was performed to determine whether titration of benazepril or losartan to optimal antiproteinuric doses would safely improve the renal outcome in chronic renal insufficiency. A total of 360 patients who did not have diabetes and had proteinuria and chronic renal insufficiency were randomly assigned to four groups. Patients received open-label treatment with a conventional dosage of benazepril (10 mg/d), individual uptitration of benazepril (median 20 mg/d; range 10 to 40), a conventional dosage of losartan (50 mg/d), or individual

uptitration of losartan (median 100 mg/d; range 50 to 200). Uptitration was performed to optimal antiproteinuric and tolerated dosages, and then these dosages were maintained. Median follow-up was 3.7 yr. The primary end point was time to the composite of a doubling of the serum creatinine, ESRD, or death. Secondary end points included changes in the level of proteinuria and the rate of progression of renal disease. Compared with the conventional dosages, optimal antiproteinuric dosages of benazepril and losartan that were achieved through uptitration were associated with a 51 and 53% reduction in the risk for the primary end point (P = 0.028 and 0.022, respectively). Optimal antiproteinuric dosages of benazepril and losartan, at comparable BP control, achieved a greater reduction in both proteinuria and the rate of decline in renal function compared with their conventional dosages. There was no significant difference for the overall incidence of major adverse events between groups that were given conventional and optimal dosages in both arms. It is concluded that uptitration of benazepril or losartan against proteinuria conferred further benefit on renal outcome in patients who did not have diabetes and had proteinuria and renal insufficiency.

Ishimitsu, T., A. Akashiba, et al. (2007). "Benazepril slows progression of renal dysfunction in patients with non-diabetic renal disease." Nephrology 12(3): 294-8.

AIM: The present study examined the effects of benazepril, an angiotensin-converting enzyme inhibitor, on the progression of renal insufficiency in patients with non-diabetic renal disease. METHODS: Fifteen patients with non-diabetic renal disease whose serum creatinine (Cr) ranged from 1.5 to 3.0 mg/dL were given either benazepril (2.5-5 mg) or placebo once daily for 1 year in a random crossover manner. In both periods, antihypertensive medications were increased if blood pressure was greater than 130/85 mmHg. Blood sampling and urinalysis were performed bimonthly throughout the study period. RESULTS: Blood pressure was similar when comparing the benazepril and the placebo periods (128+/-12/83+/-6 vs 129+/-10/83+/-7 mmHg). Serum Cr significantly increased from 1.62+/-0.18 to 1.72+/-0.30 mg/dL (P=0.036) during the placebo period, while there was no statistically significant increase in serum Cr during the benazepril period (from 1.67+/-0.17 to 1.71+/-0.27 mg/dL). The slope of decrease of the reciprocal of serum Cr was steeper in the placebo period than in the benazepril period (-0.073+/-0.067 vs-0.025+/-0.096/year, P=0.014). Urinary protein excretion was lower during the benazepril period than during the placebo period (0.57+/-0.60 vs 1.00+/-0.85 g/gCr, P=0.006). Serum K was significantly higher in the benazepril period than in the placebo period (4.4+/-0.5 vs 4.2+/-0.5 mEq/L, P<0.001), but no patient discontinued benazepril therapy as a result of hyperkalemia. CONCLUSION: Long-term benazepril treatment decreased the progression of renal dysfunction in patients with non-diabetic renal disease by a mechanism that is independent of blood pressure reduction.

Lim, S. C., A. F. Y. Koh, et al. (2007). "Angiotensin receptor antagonist vs. angiotensin-converting enzyme inhibitor in Asian subjects with type 2 diabetes and albuminuria - a randomized crossover study." Diabetes, Obesity & Metabolism 9(4): 477-82.

BACKGROUND: Subjects with type 2 diabetes mellitus (T2DM) and albuminuria are at risk for progressive diabetic nephropathy. The relative blood pressure lowering and antialbuminuric efficacy of angiotensin receptor antagonist (ARB) vs. angiotensin-converting enzyme (ACE) inhibitor has not been well studied. METHODS: Forty-one ARB- and ACE inhibitor-naive T2DM subjects with albuminuria (>30 mg/g creatinine)

were given either 50 mg of losartan (ARB) or 20 mg of quinapril (ACE inhibitor) (50% maximum dose) for 4 weeks, with a 4-week wash-out period in-between interventions in a crossover fashion. The order of intervention was randomized. The primary endpoint was the reduction of blood pressure and albuminuria. Secondary endpoint was changes in plasma transforming growth factor beta (TGF-beta). RESULTS: Among the 41 subjects, 66% were male. The mean age (s.d.) was 52 (10) years, and duration of diabetes was 8 (14) years. Blood pressure reduction (though not statistically significant) was similar on both interventions [systolic: losartan 3 (15) vs. quinapril 2 (13) mmHg, p = 0.52; diastolic: losartan 1 (9) vs. quinapril 2 (8) mmHg, p = 0.55]. However, amelioration of albuminuria [mean (s.e.)] was significantly greater with losartan [losartan vs. quinapril: -93 (82) vs. -49 (65) mg/g, p = 0.02]. There was no change in plasma TGF-beta levels [mean (s.d.)] on either treatment, losartan [before 12.1 (8.9) vs. after 11.9 (9.6) ng/ml, p = 0.68] and quinapril [11.1 (7.9) vs. 11.1 (7.8) ng/ml, p = 0.87). CONCLUSION: In Asian subjects with T2DM and albuminuria, 4 weeks of losartan therapy at 50 mg daily appeared to have greater antialbuminuric effect than 20 mg of quinapril.

Puig, J. G., M. Marre, et al. (2007). "Efficacy of indapamide SR compared with enalapril in elderly hypertensive patients with type 2 diabetes." American Journal of Hypertension 20(1): 90-7.

BACKGROUND: Blood pressure control is the main influential variable in reducing microalbuminuria in patients with type 2 diabetes. In this subanalysis of the Natrilix SR versus Enalapril Study in hypertensive Type 2 diabetics with micrOalbuminuRia (NESTOR) study, we have compared the effectiveness of indapamide sustained release (SR) and enalapril in reducing blood pressure and microalbuminuria in patients > or =65 years of age. METHODS: Of the 570 hypertensive patients with type 2 diabetes and persistent microalbuminuria in the NESTOR study, 187 (33%) individuals > or =65 years of age were included in this analysis. Of these, 95 patients received indapamide SR 1.5 mg and 92 patients received enalapril 10 mg, taken once daily in both cases. Adjunctive amlodipine and/or atenolol was added if required. RESULTS: The urinary albumin-to-creatinine ratio decreased by 46% in the indapamide SR group and 47% in the enalapril group. Noninferiority of indapamide SR over enalapril was demonstrated (P = .0236; 35% limit of noninferiority) with a ratio of 0.95 (95% CI: 0.68, 1.34). Mean arterial pressure decreased by 18 mm Hg and 15 mm Hg in the indapamide SR and the enalapril groups, respectively (P = .1136). The effects of both treatments seen in these elderly patients were similar to those observed in the main population, although the extent of the reduction in microalbuminuria was slightly higher. Both treatments were well tolerated, and no difference between groups was observed regarding glucose or lipid profiles. CONCLUSION: Indapamide SR is not less effective than enalapril in reducing microalbuminuria and blood pressure in patients aged >65 years of age with type 2 diabetes and hypertension.

Strasser, R. H., J. G. Puig, et al. (2007). "A comparison of the tolerability of the direct renin inhibitor aliskiren and lisinopril in patients with severe hypertension.[see comment]." Journal of Human Hypertension 21(10): 780-7.

Patients with severe hypertension (>180/110 mm Hg) require large blood pressure (BP) reductions to reach recommended treatment goals (<140/90 mm Hg) and usually require combination therapy to do so. This 8-week, multicenter, randomized, double-blind,

parallel-group study compared the tolerability and antihypertensive efficacy of the novel direct renin inhibitor aliskiren with the angiotensin converting enzyme inhibitor lisinopril in patients with severe hypertension (mean sitting diastolic blood pressure (msDBP)>or=105 mm Hg and <120 mm Hg). In all, 183 patients were randomized (2:1) to aliskiren 150 mg (n=125) or lisinopril 20 mg (n=58) with dose titration (to aliskiren 300 mg or lisinopril 40 mg) and subsequent addition of hydrochlorothiazide (HCTZ) if additional BP control was required. Aliskiren-based treatment (ALI) was similar to lisinopril-based treatment (LIS) with respect to the proportion of patients reporting an adverse event (AE; ALI 32.8%; LIS 29.3%) or discontinuing treatment due to AEs (ALI 3.2%; LIS 3.4%). The most frequently reported AEs in both groups were headache, nasopharyngitis and dizziness. At end point, ALI showed similar mean reductions from baseline to LIS in msDBP (ALI -18.5 mm Hg vs LIS -20.1 mm Hg; mean treatment difference 1.7 mm Hg (95% confidence interval (CI) -1.0, 4.4)) and mean sitting systolic blood pressure (ALI -20.0 mm Hg vs LIS -22.3 mm Hg; mean treatment difference 2.8 mm Hg (95% CI -1.7, 7.4)). Responder rates (msDBP<90 mm Hg and/or reduction from baseline>or=10 mm Hg) were 81.5% with ALI and 87.9% with LIS. Approximately half of patients required the addition of HCTZ to achieve BP control (ALI 53.6%; LIS 44.8%). In conclusion, ALI alone, or in combination with HCTZ, exhibits similar tolerability and antihypertensive efficacy to LIS alone, or in combination with HCTZ, in patients with severe hypertension.

Tumanan-Mendoza, B. A., A. L. Dans, et al. (2007). "Dechallenge and rechallenge method showed different incidences of cough among four ACE-Is." Journal of Clinical Epidemiology 60(6): 547-53.

OBJECTIVE: To determine the incidence of cough secondary to (1) Cilazapril, (2) Enalapril, (3) Imidapril, and (4) Perindopril and their efficacy in the control of hypertension. STUDY DESIGN AND SETTING: Randomized double-blind study conducted in selected medical centers in the Philippines from the first quarter of 1999 to March, 2001. RESULTS: A total of 301 patients, aged 28-86 years with stage I or II hypertension were included. Patients were randomized to Cilazapril 2.5-5.0 mg/day (n=70), Enalapril 10-20 mg/day (n=82), Perindoril 4-8 mg/day (n=73), or Imidapril 10-20 mg/day (n=76). Hydrochlorothiazide 12.5 mg/day was added if needed. Using a dechallenge and rechallenge method, a strict criteria to attribute cough to angiotensin converting enzyme inhibitors (ACE-Is) not yet used in previous reports, the cough incidence were as follows: (1) Cilazapril--22.86% (16/70), (2) Enalapril--21.95% (18/82), (3) Perindopril--10.96% (6/73), and (4) Imidapril--13.16% (10/76) (P=0.041). Control of hypertension was significantly better with Enalapril during the first follow-up period. CONCLUSION: Statistically significant differences in the incidence of cough among the studied ACE-Is were noted. Control of hypertension was observed to be better in those with a higher incidence of cough; however, the mean change of both systolic and diastolic blood pressure levels were not significantly different.